Remarks

Applicants appreciate the Examiner's helpful comments regarding the restriction, and confirm the election of the claims of Group I (claims 1–16) as indicated. Clams 17–20 are presently withdrawn and cancelled by amendment to advance the prosecution of the present application, with the proviso that the presently cancelled claims may be later prosecuted in a continuation or divisional application.

Claims 1, 2, 4, 6, 10, 11, 13 and 14 are amended to more clearly define the subject matter which Applicants regard as the invention. Claims 21 and 22 are newly added. Support for amendments to the claims can be found in the claims or the specification as originally filed. Specifically, support for weight ranges recited at claims 10, 21 and 22 can be found in the specification at paragraph [0222] and Table 4. No new matter has been added.

Regarding Review of All IDS References Submitted by Applicants

Applicants also wish to inquire why a reference cited by the Examiner in the Office Action and previously submitted by Applicants in an Information Disclosure Statement has not been reviewed by the Examiner. Specifically, item No. 96 on PTO/SB/08A filed with the U.S.P.T.O. on November 12, 2007, a copy of which was presented with the present Action, was not initialed by the Examiner, although every other reference has been initialed. Moreover, the reference is marked "not reviewed" on the margin of the sheet next to the reference title. Applicants are confused, especially given that the reference is cited by the Examiner in the present Office Action. Has the referenced indeed been reviewed? If so, Applicants request that the Examiner kindly initial the reference identifier and reissue a copy of the document indicating that all documents have been reviewed.

Regarding Applicants' Rights to Benefit from the Effective Filing Date of USSN 09/460,605

The Examiner has raised an issue regarding Applicants' claim to the benefit of the filing date of Application No. 09/460,605, now U.S. Patent No. 6,835,394. According to the Examiner, the present application does not have support for the claims because there is no mention of the elected species. Applicants respectfully disagree, and guide the Examiner to Col. 5, lines 15 – 21 of U.S. Patent No. 6,835,394, where support for the elected species of a PEO-

butadiene block copolymer is found. Thus, because Applicants' present application is a continuation-in-part, repeating some substantial portion of the earlier nonprovisional application filed December 14, 1999, and adds new matter not previously disclosed, the continuation-in-part is entitled to the benefit of the filing date of the earlier nonprovisional application (now U.S. Patent No. 6,835,394) in accordance with MPEP 210.08.

As such, Applicants' benefit of an earlier filing date claims priority over references cited by the Examiner, specifically Discher *et al., J. Phys. Chem. B.*, 2002, which was published 3 years after Applicants' priority date of December 14, 1999.

Response to the Rejection under 35 U.S.C. § 112, second paragraph:

Claims 1 – 16 have been rejected for failing to point out and distinctly claim the subject matter which Applicants regard as the invention. In making this rejection, the Examiner asserts that Claim 1 is indefinite for reciting "high molecular weight" because it is not clear what molecular weights are "high" as recited. Applicants guide the Examiner to Table 1 of the specification, which lists representative molecular weight ranges of PEO-based polymersomes. Paragraph [0072] discusses encapsulating membranes of the present invention, which clearly exceed the "many kilodaltons range." Furthermore, paragraph [0077] expressly provides the preferred molecular weight range for polymersomes of the present invention of 1400 to 8700 g/mol. Thus, Applicants respectfully assert that appropriate guidance is given as to "high" molecular weight ranges.

Claim 2 is rejected by the Examiner for the use of "a structural equivalent thereof"; however, in light of the amendment to Claim 2 this point of the rejection is now moot.

Claim 4 is rejected for the same reason stated above for claim – the Examiner contends that it is not clear which molecular weights are "high." For the same reasons as discussed above for claim 1, Applicants maintain that the specification provides clear guidance as to "high molecular weight" polymersomes of the present invention.

Claim 6 is rejected for the use of mole faction and mole % in the claim. Indeed, Applicants acknowledge the difference in their meaning, and have amended the claim to properly reflect that it is the mol % that is adjustable. For instance, in the specification at paragraph [0244], an example is provided of "25:75 mole % blends." Thus, a polymersome in accordance with Applicants' method could be prepared by combining degradable polymer to inert polymer,

at a ratio of 25:75, where the total of the two subcomponents equals 100 total moles. Thus, in light of the amendment to claim 6, the rejection is now moot.

Claim 10 is rejected by the Examiner as being indefinite for reciting a range without an upper or lower limit. Applicants respectfully assert that in light of the amendment to claim 11, the rejection is now moot.

Claim 11 is rejected because the Examiner contents that the claim language as presented, with the recitation that f_{EO} and polyester selection "primarily dictate release kinetics" and the recitation that molecular weight of encapsulant will "decelerate rate of release" is incompatible. Applicants respectfully assert that in light of the amendment to claim 11, the rejection is now moot.

Claims 13 and 14 are rejected by the Examiner for the use of "including" in a Markush group. Applicants respectfully assert that in light of the amendment to claims 13 and 14, the rejection is moot.

In sum, Applicants respectfully assert that the claims, as amended, particularly point out and distinctly claim the subject matter which Applicants regard as their invention. As such, Applicants request that the rejection under 35 U.S.C. § 112, second paragraph be reconsidered and withdrawn.

Response to the Rejection under 35 U.S.C. § 103(a):

Claims 1–16 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Piskin et al, in view of Won *et al.*, and in further view of Discher *et al.* For the reasons stated above regarding the priority issue raised by the Examiner, Applicants respectfully assert that the 2002 Discher reference is not proper prior art with regard to Applicants' invention because the cited reference was published three years after the priority date of Applicants' present application. Thus, Discher cannot be used by the Examiner to support a rejection under § 103(a), and Applicants ask that it be withdrawn.

Nevertheless, in making the rejection, the Examiner states it would have been prima facie obvious to a person of ordinary skill in the art at the time of the invention to make a mixed micelle of PEG-PLA and PEG-PBD by blending the two in aqueous solution to encapsulate doxorubicin within the resulting micelle. The Examiner cites Piskin for teaching copolymer micelles made from PEG-PLA used to encapsulate doxorubicin, with release of the drug controlled by degradation of the PLA component of the micelles. However, the Examiner then

continues by pointing out that Piskin fails to teach or suggest blending PEG-PLA with PEG-PBD to form micelles. To bridge the gap between Piskin and Applicants' disclosed invention, the Examiner relies on Won and Discher, but Applicants traverse such a conclusion.

Even if combined, the cited references fail to teach or suggest Applicants' invention. Not only does Piskin not teach blending PEG-PLA with PEG-PBD to form micelles, as admitted by the Examiner, Piskin does not teach the formation of self-assembling bi-layer membranes - *i.e.*, polymersomes – as taught by Applicants. What Piskin actually teaches are micelles formed by transesterification of PLA with PEG, resulting in small, packed micelles with a PLA core and PEG outer shell. (See Piskin, page 361-362, which describe esterification and Figures 1 and 10 which show the resulting structure of the PLA-PEG micelles.)

In marked contrast, Applicants' polymersomes do not require esterification for assembly. Polymersomes, as taught by Applicants, self-assemble into a closed membrane bi-layer in aqueous solution *without* the need for additional organic solvents or chemical processes. Moreover, esterified micelles as taught by Piskin have a different membrane structure and different chemical properties than the synthetic copolymer polymersomes that self-assembled into a membrane bi-layer, as expressly claimed by Applicants.

Although the Piskin micelles are capable of releasing encapsulated material, such release occurs at the expense of micelle degradation and results in a subsequent loss in overall structural integrity. On the contrary, polymersomes release encapsulated material through poration of the membrane, which occurs locally within the membrane, as disclosed in Applicants' specification at paragraphs [0257], [0258]. Release of encapsulated material in Applicants' invention, therefore, is a direct result of blending an appropriate amount of diblock copolymers, such that the ratio of hydrophobic portion to hydrophilic portion of the polymersomes drives release kinetics. Thus, the mechanism for release and the structure, formulation and formation of the Piskin micelle are entirely different from Applicants' method of forming a polymersome of selected component copolymers that when blended provides a controlled rate of release of the at least one encapsulant contained therein.

Accordingly, Piskin fails as a §103(a) reference because one skilled in the art relying upon Piskin's method for esterification of PEG or PLA to prepare stable, synthetic, self-assembling polymersomes according to Applicants' invention, which requires the steps of previously determined and preselected the necessary blend of hydrophobic and hydrophilic

polymers at a ratio that provides a controlled rate of release of the at least one encapsulant contained therein. Moreover, there is no suggestion or motivation to modify Piskin to arrive at the polymersomes of Applicants' invention because one skilled in the art would recognize the *structural* and *functional* differences between the micelles taught by Piskin and understand that they could not produce the controlled release polymersomes having the characteristics required by Applicants' invention.

The Examiner further cites Won for teaching that PEG-PBD is useful in making micelles, and asserts that one skilled in the art would have sought to combine known materials for the same purpose, such as disclosed in Piskin. However, not only does Piskin fail to provide micelles equivalent to or suggestive of Applicants' polymersomes containing a preselected ration of blended copolymers, when read carefully, Won teaches giant worm-like micelles with a PEO volume fraction of over 47 percent. Thus, the Won micelles are described as "rubber"-like, meaning thick-walled (see Won, page 961, first column and page 962, middle column), and having exceptional stability. By comparison as expressly stated in claim 1, Applicants' controlled release polymersome are necessarily thin-walled. Also, see Won at Figures 1 and 2, which show long, worm-like structures which are clearly not the polymersomes as taught by Applicants, having a PEO volume fraction of between 25% and 42%. See Applicants' disclosure at [0043].

The structure, shape and function of micelles taught by Won are entirely different from the thin-walled, bi-layer, closed membrane structure of the polymersomes taught by Applicants. Moreover, because the wormlike-micelles taught by Won comprise primarily *inert* PBD, they lack a controllable hydrolytic component of Applicants' invention. In fact, without a hydrolytic component of a copolymer, the Won micelles are so stable that they are incapable of controlled release of encapsulated material. To the contrary, however, the formulation of Applicants' controlled release polymersomes requires as a claimed essential element, expressly determining, selecting and blending an appropriate ratio of hydrolysable copolymer with hydrophobic copolymer to provide the desired controlled release kinetics.

Consequently, neither Piskin nor Won, alone or in combination, could have or would have taught one of ordinary skill in the art, at the time of the invention, a method of preparing self-assembling, *controlled release* polymersomes in accordance with Applicants' invention. Even if combined, Piskin and Won fail to teach how to determine the appropriate blend ratio of

hydrophilic copolymer to hydrophobic copolymer, and how to blend copolymers in aqueous solution to produce amphiphilic high molecular weight PEO-based polymersomes having a desired controlled release rate. Moreover, absent Applicants' own specification, a practitioner would not suspect or know why the expressly claimed step in Applicants' formulation for predetermining the blend ratio would be relevant to expressly controlling the release rates of an encapsulated material from the resulting polymersome.

The Examiner relies on Discher for suggesting blending of PEG-PBD with another PEG-based diblock copolymer to make mixed micelles. Of course, as noted above, Discher is not a proper reference for prior art purposes and cannot be used in making the §103(a) rejection. Nevertheless, even if Discher were properly applied as a reference, it does not provide the necessary teaching or suggestion to lead one skilled in the art to combine the teachings of Piskin and Won to arrive at Applicants' invention in a manner asserted by the Examiner.

Discher teaches vesicles designated as OB2, which are merely giant unilamellar vesicles formed from polymers of ethylene oxide (EO) linked to long chains of butadiene. See Discher, page 2849 and Fig. 1. Thus, Discher teaches a vesicle with similar viscoelastic properties found in the worm micelles taught by Won. The only other vesicle mentioned in Discher is OE7, a non-crosslinkable analog. Nowhere in Discher is a method of determining the appropriate blend ratio – mol % - of hydrolysable component and inert component for allowing self-assembly of polymersomes that provide controlled release kinetics of encapsulant, as taught by Applicants' claim 1. Thus, Discher fails to bridge the gap between Piskin and Won, and combined the cited references could not lead one of ordinary skill in the art to Applicants' invention.

At the time of Applicants' invention, preparing a stable, self-assembling polymersome blended expressly to provide the necessary controlled release kinetics for releasing an active agent contained therein, specifically by determining and selecting the appropriate blend ratio of hydrophilic/hydrolysable component to hydrophobic/inert component, was not known to one of ordinary skill in the art. When attempting to prepare polymersomes capable of controlled release of an encapsulant, one of ordinary skill in the art would not have been led to either Piskin and/or Won because both each provides teach thick-walled, stable micelles – not polymersomes – having entirely different membrane structure, function, release properties and membrane integrity. While the Discher reference may form micelles comprising PEG and PBD with another PEG copolymer, such information would have been useless to the practitioner in forming

the controlled release polymersomes of Applicants' invention – unless they were also provided with Applicants' specification. It is Applicants' specification that expressly teaches why and how the blended ratio of hydrophobic to hydrophilic components is the determinative step for controlling the rate of release of an encapsulant therein. This is not simply functional information, but rather the basis for conducting the claimed determining and selecting steps for preparing the blend ratio. Of course, such hindsight reasoning based upon Applicants' own specification is impermissible under the law for forming a rejection under §103.

Contrary to known uses of PEG lipids to impart stealth-ness, at the time of the invention there were no known compositions in which the hydrophobic part of the PEG lipid degrades, or in which the PEG chains were designed to degrade in order to trigger controlled release of an encapsulant. Using polymers to achieve controlled release in the manner of Applicants' invention was not known, primarily because polyesters are oxygen-rich. Therefore, only when a polymer chain is made long enough, as taught in Applicants' present invention, will it be sufficiently hydrophobic to drive polymersome vesicle assembly. Accordingly, the state of the art at the time of the invention negates the proposed motivation offered by the Examiner in the cited combination of references.

Moreover, the cited references, alone or in any combination, are deficient in that they fail to teach or suggest each and every element of Applicants' claimed invention. Specifically, even in combination, the references fail to teach a method of determining, selecting and preparing a controlled release polymersome, comprising a bled of hydrophobic and hydrophilic copolymers in a manner such that the mol %, and resulting PEO volume fraction determine and drive controlled release kinetics of an encapsulate contained in the polymersome, as expressly taught by Applicants' claims 1 – 16. As such, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

Conclusion

In view of the foregoing, Claims 1 – 16, and newly added claims 21 and 22 are in condition for allowance. Prompt and favorable consideration to this Amendment and Reply is respectfully requested.

Should the Examiner have any questions or comments regarding Applicants' amendments or response, the Examiner is asked to contact Applicants' undersigned representative at (215) 772-7550.

Respectfully submitted,

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Evelyn H. McConathy
Registration No. 35,279
MONTGOMERY, McCRACKEN,
WALKER & RHOADS, LLP
123 South Broad Street
Philadelphia, PA 19109-1099
Tel: (215) 772.7550
Fax: (215) 772.7620